

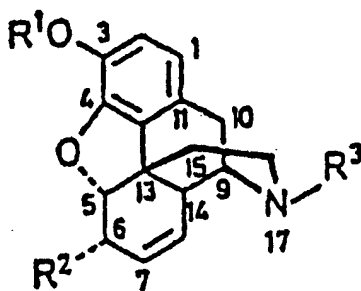
AMENDMENTS TO THE CLAIMS:

Please replace the claims with the claims provided in the listing below wherein status, amendments, additions and cancellations are indicated.

Claim 31. (New) Morphine alkaloid acid addition salt consisting essentially of:

an acid addition salt formed by the reaction of:

A) at least one morphine alkaloid of formula I



(I)

where R^1 is selected from the group consisting of: H, and C_1 to C_6 alkyl;

R^2 is selected from the group consisting of: H, OH, $OC(O)CH_3$, $=O$, and $=CH_2$, such that when R^2 is H, OH, or $OC(O)CH_3$, a fourth valence bond at the C (6) position in formula I is H;

R^3 is selected from the group consisting of: CH_3 , cyclopropyl, cyclobutyl, and allyl;

the bond between the C (7) and C (8) positions in formula I is alternatively saturated; and

alternatively there is a nitroxyl group at the N (17) position in formula I; with

- B) at least one organic acid selected from the group consisting of:
- a) an acid that is an equilibrium product of a mixture of a monoester of a C_3 to C_{16} dicarboxylic acid and a monohydric C_1 to C_4 alcohol;
 - b) C_2 to C_{16} sulfonic acids;
 - c) a substituted benzoic acid selected from the group consisting of: halogen, hydroxy, alkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, and amino substituted benzoic acid;
 - d) 5- and 6-member ring heterocyclic compounds having at least one N or S atom, with unsaturated and saturated rings, and unsubstituted, and substituted with one of: a carboxyl group, unbranched and branched carboxypropyl, and unbranched and branched carboxybutyl;
 - e) C_5 to C_{10} oxocarboxylic acids, unsaturated and saturated, and unsubstituted and substituted;
 - f) phenyl-substituted and phenoxy-substituted saturated C_2 to C_4 carboxylic acids; and

- g) aliphatic, aromatic, and heterocyclic C₂ to C₁₂ amino acids, and aliphatic, aromatic, and heterocyclic C₂ to C₁₂ (mono) amino acids and (poly) amino acids (polypeptides), wherein at least one amino group is substituted with one of:
- i) an unsubstituted C₂ to C₆ alkanoyl group,
 - ii) a substituted C₂ to C₆ alkanoyl group,
 - iii) an unsubstituted benzoyl group, and
 - iv) a substituted benzoyl group.

Claim 32. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said morphine alkaloid is selected from the group consisting of: morphine, codeine, heroin, ethylmorphine, levorphanol, hydromorphone, and mixtures of any of the foregoing.

Claim 33. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said monoester in (B)(1) is of a C₅ - C₁₀ dicarboxylic acid.

Claim 34. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said monoester in (B)(1) is monomethylsebacate.

Claim 35. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said dicarboxylic acid in (B)(1) is selected from the group consisting of: suberic acid, azelaic acid, and sebacic acid.

Claim 36. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said alcohol in (B)(1) is methanol.

Claim 37. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said sulfonic acid in (B)(2) is a C₄ to C₈ sulfonic acid.

Claim 38. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said sulfonic acid in (B)(2) is hexanesulfonic acid.

Claim 39. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said alkyl, hydroxyalkyl, and alkoxy groups, and one or both of alkyl and alkoxy portions of said alkoxyalkyl groups of said substituted benzoic acids in (B)(3) are C₁ to C₁₂.

Claim 40. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said alkyl and alkoxy groups, and one or both of alkyl and alkoxy portions of said alkoxyalkyl groups of said substituted benzoic acids in (B)(3) are branched.

Claim 41. (New) Morphine alkaloid acid addition salt according to claim 40, wherein said branched alkyl and alkoxy groups are selected from the group consisting of : i-propyl, 2-methylpropyl, t-butyl, and 2-methylbutyl.

Claim 42. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said substituted benzoic acid in (B)(3) is polysubstituted.

Claim 43. (New) Morphine alkaloid acid addition salt according to claim 42, wherein said polysubstitution is with at least one of C₁ to C₁₂ unbranched and branched alkyl and alkoxy groups.

Claim 44. (New) Morphine alkaloid acid addition salt according to claim 31, wherein an alkoxy portion of an alkoxyalkyl group of said alkoxyalkyl substituted benzoic acid in (B)(3) is C₁ to C₆.

Claim 45. (New) Morphine alkaloid acid addition salt according to claim 44, wherein said alkoxy portion of said alkoxyalkyl groups is selected from the group consisting of: methyloxy, ethyloxy, and propyloxy.

Claim 46. (New) Morphine alkaloid acid addition salt according to claim 44, wherein said alkoxy portion is etherified with C₁ to C₄ hydroxyalkyl.

Claim 47. (New) Morphine alkaloid acid addition salt according to claim 44, wherein said C₁ to C₄ hydroxyalkyl is selected from the group consisting of: hydroxymethyl, hydroxyethyl, and hydroxypropyl.

Claim 48. (New) Morphine alkaloid acid addition salt according to claim 31, wherein an amino group of said amino substituted benzoic acid in (B)(3) is alkylated.

Claim 49. (New) Morphine alkaloid acid addition salt according to claim 48, wherein alkylation of said amino group is with a C₁ to C₄ alkyl group.

Claim 50. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said substituted benzoic acid in (B)(3) is selected from the group consisting of:

C₁ to C₆ alkyl, hydroxy-(C₁ to C₆)-alkyl, amino, and hydroxy substituted benzoic acids.

Claim 51. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said substituted benzoic acid in (B)(3) is an amino-substituted benzoic acid.

Claim 52. (New) Morphine alkaloid acid addition salt according to claim 51, wherein said amino-substituted benzoic acid is aminobenzoic acid.

Claim 53. (New) Morphine alkaloid acid addition salt according to claim 52, wherein an amino group of said aminobenzoic acid is one of: unsubstituted, and substituted.

Claim 54. (New) Morphine alkaloid acid addition salt according to claim 52, wherein said substituted amino group of said aminobenzoic acid is one of: monosubstituted, and disubstituted.

Claim 55. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said alkyl substituted benzoic acid in (B)(3) is a monosubstituted or polysubstituted C₁ to C₄ alkyl benzoic acid.

Claim 56. (New) Morphine alkaloid acid addition salt according to claim 55, wherein said polysubstituted C₁ to C₄ alkyl benzoic acid is tri-substituted.

Claim 57. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said hydroxyalkyl-substituted benzoic acid in (B)(3) is selected from the group consisting of: hydroxymethyl benzoic acid, hydroxyethyl benzoic acid, hydroxypropyl benzoic acid, and hydroxybutyl benzoic acid.

Claim 58. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said hydroxy-substituted benzoic acid is selected from the group consisting of: p-hydroxy benzoic acid, and m-hydroxy benzoic acid.

Claim 59. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said substituted benzoic acid in (B)(3) is selected from the group consisting of: p-hydroxybenzoic acid, p-aminobenzoic acid, and trimethylbenzoic acid.

Claim 60. (New) Morphine alkaloid acid addition salt according to claim 59, wherein said trimethylbenzoic acid is 2,4,6-trimethylbenzoic acid.

Claim 61. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said 5- and 6-member ring heterocyclic compound having at least one N or S atom in (B)(4) is selected from the group consisting of: pyridine, piperidine, pyrimidine, pyrrole, and thiophene.

Claim 62. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said unsubstituted and substituted 6-member ring heterocyclic compound having at least one N or S atom in (B)(4) is a pyridinecarboxylic acid.

Claim 63. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said unsubstituted and substituted 5-member ring heterocyclic compound having at least one N or S atom in (B)(4) is lipoic acid.

Claim 64. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said C₅ to C₁₀ oxocarboxylic acid in (B)(5) is selected from the group consisting of: 2-oxocarboxylic acid, 4-oxocarboxylic acid, 5-oxocarboxylic acid, and 9-oxocarboxylic acid.

Claim 65. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said C₅ to C₁₀ oxocarboxylic acid in (B)(5) is selected from the group consisting of: 5-oxopyrrolidine-2-carboxylic acid (pyroglutamic acid), levulinic acid, and oxo-dec-2-ene acid.

Claim 66. (New) Morphine alkaloid acid addition salt according to claim 31, wherein a C₂ to C₄ carboxylic acid of said phenyl-substituted and said phenoxy-substituted saturated C₂ to C₄ carboxylic acid in (B)(6) is selected from the group consisting of: acetic acid, propionic acid, and butyric acid.

Claim 67. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said aliphatic, aromatic, and heterocyclic C₂ to C₁₂ amino acid in (B)(7) is a monoaminomonocarboxylic acid, wherein an amino group is substituted with one of:

a C₂ to C₆ alkanoyl group, which is monosubstituted or polysubstituted with one selected from the group consisting of: hydroxy, C₁ to C₄ alkoxy, C₁ to C₄ hydroxyalkyl; and

a benzoyl group, which is monosubstituted or polysubstituted with one selected from the group consisting of: C₁ to C₄ alkyl, C₁ to C₄ alkoxy, C₁ to C₄ hydroxyalkyl, halogen, amino, and hydroxy.

Claim 68. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said aromatic amino acid in (B)(7) is a phenyl amino acid.

Claim 69. (New) Morphine alkaloid acid addition salt according to claim 68, wherein said phenyl amino acid is selected from the group consisting of: phenylalanine, and tyrosine.

Claim 70. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said heterocyclic amino acid in (B)(7) is selected from the group consisting of: proline, hydroxyproline, and tryptophan.

Claim 71. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said aliphatic amino acid in (B)(7) is an aliphatic C₂ to C₆ monoaminomonocarboxylic acid.

Claim 72. (New) Morphine alkaloid acid addition salt according to claim 71 wherein said amino group of said aliphatic C₂ to C₆ monoaminomonocarboxylic acid is substituted with one of: an acetyl group, and a benzoyl group.

Claim 73. (New) Morphine alkaloid acid addition salt according to claim 31, having a molecular weight less than 800.

Claim 74. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said salt is a mixture of the reaction products of one of:

- I. one morphine alkaloid of formula I in (A), with one organic acid in (B);
- II. one morphine alkaloid of formula I in (A), with a plurality of organic acids in (B);
- III. a plurality of morphine alkaloids of formula I in (A), with one organic acid in (B); and
- IV. a plurality of morphine alkaloids of formula I in (A), with a plurality of organic acids in (B).

Claim 75. (New) Morphine alkaloid acid addition salt according to claim 31, wherein said at least one organic acid in (B) is a pharmaceutically acceptable organic acid.

Claim 76. (New) Composition comprising:

morphine alkaloid acid addition salt according to claim 74; and
one of: a solvent therefor, and a suspension medium therefor.

Claim 77. (New) Composition according to claim 76, wherein said solvent or said suspension medium is selected from the group consisting of: glycerol, ethylene glycol, oleic acid, dimethylisosorbide, dimethylsulfoxide, and olive oil.

Claim 78. (New) Composition according to claim 74 for transdermal administration, further comprising a skin penetration enhancer.

Claim 79. (New) Composition according to claim 78, wherein said skin penetration enhancer is selected from the group consisting of: a polyoxethylene sorbitane fatty acid, a polyoxethylene alcohol, and mixtures thereof.

Claim 80. (New) Composition according to claim 74, in a form selected from the group consisting of: lotion, ointment, cream, gel, aerosol spray, transdermal therapeutic system (TTS), transmucosal therapeutic system, and iontophoretic device.

Claim 81. (New) Composition according to claim 80, as a TTS.

Claim 82. (New) Composition according to claim 81, wherein said TTS comprises:

a backing layer, impermeable to said composition; and

a reservoir layer comprising:

40 - 80 wt% of a polymer material selected from the group

consisting of: a polyacrylate, a polystyrene, and a silicone;

0.1 - 30 wt% of a plasticizer; and

0.1 to 30 wt% of said morphine alkaloid acid addition salt.

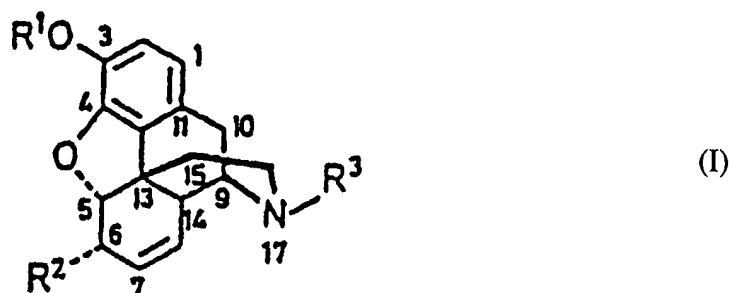
Claim 83. (New) Composition according to claim 82, wherein said backing layer is a flexible or a non-flexible material.

Claim 84. (New) Composition according to claim 82, wherein said backing layer is a composite material.

Claim 85. (New) Composition according to claim 82, wherein material of said backing layer is selected from the group consisting of: polymer film, metal foil, polymer-coated metal foil, textile fabric impenetrable to components of said reservoir layer.

Claim 86. (New) Method of forming a morphine alkaloid acid addition salt, comprising the steps of:

A) providing a solution of a morphine alkaloid of formula I



where R^1 is selected from the group consisting of: H, and C_1 to C_6 alkyl;

R^2 is selected from the group consisting of: H, OH, $OC(O)CH_3$, $=O$, and $=CH_2$, such that when R^2 is H, OH, or $OC(O)CH_3$, a fourth valence bond at the C (6) position in formula I is H;

R^3 is selected from the group consisting of: CH_3 , cyclopropyl, cyclobutyl, and allyl;

the bond between the C (7) and C (8) positions in formula I is alternatively saturated; and

alternatively there is a nitroxyl group at the N (17) position in formula I; in an appropriate solvent therefor;

B) providing one of a liquid organic acid and a solution of an organic acid, selected from the group consisting of:

1) an acid that is an equilibrium product of a mixture of a monoester of a C_3 to C_{16} dicarboxylic acid and a monohydric C_1 to C_4 alcohol;

- 2) C_2 to C_{16} sulfonic acids;
- 3) a substituted benzoic acid selected from the group consisting of:

halogen, hydroxy, alkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, and amino substituted benzoic acid;
- 4) 5- and 6-member ring heterocyclic compounds having at least one N or S atom, with unsaturated and saturated rings, and unsubstituted, and substituted with one of: a carboxyl group, unbranched and branched carboxypropyl, and unbranched and branched carboxybutyl;
- 5) C_5 to C_{10} oxocarboxylic acids, unsaturated and saturated, and unsubstituted and substituted;
- 6) phenyl-substituted and phenoxy-substituted saturated C_2 to C_4 carboxylic acids; and
- 7) aliphatic, aromatic, and heterocyclic C_2 to C_{12} amino acids, and aliphatic, aromatic, and heterocyclic C_2 to C_{12} (mono) amino acids and (poly) amino acids (polypeptides), wherein at least one amino group is substituted with one of:
 - a) an unsubstituted C_2 to C_6 alkanoyl group,
 - b) a substituted C_2 to C_6 alkanoyl group,

- c) an unsubstituted benzoyl group, and
 - d) a substituted benzoyl group;
- C) reacting (A) and (B) to form said morphine alkaloid acid addition salt therefrom; and
- D) isolating said morphine alkaloid acid addition salt.

Claim 87. (New) Method of forming a transdermal delivery system for a morphine alkaloid acid addition salt, comprising the steps of:

- A) providing a morphine alkaloid acid addition salt according to the method of claim 115;
- B) forming a mixture by mixing a therapeutically effective amount of said morphine alkaloid acid addition salt with components of a reservoir layer of said transdermal delivery system, said components comprising:
 - a polymer material selected from the group consisting of:
rubber, synthetic homopolymers having rubber-like properties, synthetic copolymers having rubber-like properties, synthetic block polymers having rubber-like properties, polyacrylic acid esters, copolymers of polyacrylic acid esters, polyurethanes, and silicones;

a plasticizer;

a solvent; and

up to each of an additive selected from the group consisting

of: tackifying agent, stabilizer, carrier, and filler;

- C) applying said mixture formed in (B) to a backing layer to form a matrix reservoir layer containing said morphine alkaloid acid addition salt therein on said backing layer;
- D) removing said solvent; and
- E) applying a protective layer to said matrix reservoir layer.